Naturally occurring mutations in the human **5-lipoxygenase gene** promoter that modify transcription factor binding and reporter gene transcription.

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AB Five lipoxygenase (5-LO) is the first committed enzyme in the metabolic pathway leading to the synthesis of the leukotrienes. We examined genomic DNA isolated from 25 normal subjects and 31 patients with asthma (6 of whom had aspirin-sensitive asthma) for mutations in the known transcription factor binding regions and the protein encoding region of the **5-LO gene**. A family of mutations in the G + C-rich transcription factor binding region was identified consisting of the deletion of one, deletion of two, or addition of one zinc finger (Sp1/Egr-1) binding sites in the region 176 to 147 bp upstream from the ATG translation start site where there are normally 5 Sp1 binding motifs in tandem. Reporter gene activity directed by any of the mutant forms of the transcription factor binding region was significantly ($P < 0.05$) less effective than the activity driven by the wild type transcription factor binding region. Electrophoretic mobility shift assays (EMSAs) demonstrated the capacity of wild type and mutant transcription factor binding regions to bind nuclear extracts from human umbilical vein endothelial cells (HUVECs). These data are consistent with a family of mutations in the **5-LO gene** that can modify reporter gene transcription possibly through differences in Sp1 and Egr-1 transactivation.

1998-01616 BIOTECHDS

TITLE: Classifying patients with inflammatory disease, specifically asthma;
disease diagnosis and estimation of suitability of therapy

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PATENT ASSIGNEE: Brigham+Women's-Hosp.Boston

LOCATION: Boston, MA, USA.

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AB A new method for classifying patients suffering from inflammatory disease involves: identifying in DNA from at least 1 patient a sequence **polymorphism**, as compared with the normal 5-lipoxygenase (EC-1.13.11.12) gene, in a **5-lipoxygenase gene** regulatory sequence; and classifying the patient based on the identified **polymorphism**. The inflammatory disease is asthma, ulcerative colitis, sinusitis, psoriasis, allergic and non-allergic rhinitis, lupus or rheumatoid arthritis. The sequence **polymorphism** is addition or deletion of a binding site (Sp1 or Egr-1 site) for a transcriptional activator or repressor expressed in white blood cells or is a substitution or mutation which disrupts the binding site. Also new are: identification of an asthma patient who is a candidate for therapy with 5'-lipoxygenase-inhibitors by comparing the level of 5-lipoxygenase with that of a healthy person or by detecting a **5'-lipoxygenase gene** mutation; identification of a person susceptible to inflammatory disease, which involves detecting a DNA **polymorphism** in the **5-lipoxygenase gene** from the person. (56pp)

99365912 PubMed ID: 10436859

TITLE: Mutations in the human **5-lipoxygenase gene.**

AUTHOR: In K H; Silverman E S; Asano K; Beier D; Fischer A R; Keith T P; Serino K; Yandava C; De Sanctis G T; Drazen J M

CORPORATE SOURCE: Department of Medicine, Brigham and Women's Hospital, Boston, MS, USA.

SOURCE: CLINICAL REVIEWS IN ALLERGY AND IMMUNOLOGY, (1999 Spring-Summer) 17 (1-2) 59-69.
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AB Our data demonstrate the presence of a naturally occurring family of alleles in the core promoter of the **5-LO gene** , which is characterized by the deletion or addition of consensus Sp1 (-GGGCGG) and Egr-1 (-GCGGGGGCG-) binding motifs. Each of the **variant** alleles can bind Sp1 and Egr-1 protein, as indicated by EMSA and supershift analysis with nuclear extracts. In addition, preliminary data from CAT reporter assays indicate that these alleles are less effective than the wild-type allele in initiating **5-LO gene** expression. Whether patients harboring the various alleles identified herein have different capacities to transcribe the **5-LO gene** and the importance of such potential regulation to the clinical expression of 5-LO have yet to be determined.

Genetic **polymorphisms** of 5-LO

AUTHOR(S): Silverman, Eric S.; In, Kwang H.; Collins, Tucker; Drazen, Jeffrey M.

CORPORATE SOURCE: Pulmonary and Critical Care Division, Department of Medicine, Vascular Research Division, Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA

SOURCE: Novel Inhibitors of Leukotrienes (1999), 147-164. Editor(s): Folco, Giancarlo; Samuelsson, Bengt; Murphy, Robert C. Birkhaeuser Verlag: Basel, Switz. CODEN: 68HHAI

DOCUMENT TYPE: Conference; General Review

LANGUAGE: English

AB A review with 43 refs. on 5-lipoxygenase (**5-LO**) **gene** regulation and how this regulation may be altered by naturally occurring promoter mutations. Topics include: regulation of 5-LO; **5-LO gene** transcription; naturally occurring 5-LO promoter mutations in healthy and asthmatic humans; and Sp1 and Egr-1 interactions in gene transcription.

Asthma pharmacogenetics

AUTHOR(S): Drazen, Jeffrey M.
CORPORATE SOURCE: Women's Hospital, Brigham, UT, USA
SOURCE: Pharmaceutical News (2000), 7(6), 26-31
CODEN: PHNEEP; ISSN: 1071-894X
PUBLISHER: G+B Magazines
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 33 refs. Topics discussed include the definition of asthma; treatments for asthma including bronchodilators, inhaled corticosteroids and anti-leukotrienes; pharmacogenetic mechanisms of asthma; repeatability of treatment responses; **polymorphism** of the .beta.2-adrenergic receptor; and **polymorphism** of the 5-**lipoxygenase gene** promoter.